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Legal Department
Incyte Genomics
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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,335	TANG ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) *21 and 29-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group 4, claims 3-6, 9-14, SEQ ID NO:4 in Paper of 02/17/04 is acknowledged and entered.

Applicant cancels claims 1-20 and adds new claims 21-40. New claims 22-28 correspond to the elected claims 3-6, 9-14.

Claims 21-40 are pending in the instant application and Claims 21, 29-40 has been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group 4, Claims 22-28, SEQ ID NO:4, are currently under prosecution.

The traversal is on the following ground(s):

1) Applicant asserts that the polypeptide of SEQ ID NO:2 and the polynucleotide of SEQ ID NO:4, encoding SEQ ID NO:2 meet the unity of invention requirement according to Example 17, part 2 of Annex B to the Administrative instructions under the PCT.

2) Applicant asserts that dependent claims drawn to antibodies should also examined together with the polypeptide.

3) Applicant asserts that all the claims, including the methods claims should be examined, because there is unity of invention among all the claims, having the claimed polynucleotides and the encoded polypeptides as the corresponding technical features that are common to all the claims.

4) It is a minimum burden to examine the newly added claims 29-30, which belong to group 6, claims 34,35, which are drawn to methods of using the elected

polynucleotides, and claims 36-37 which are drawn to microarrays, using the elected polynucleotides, and

5) The methods claims should be rejoined with the composition claims upon allowance of the product claims in light of *In re Ochiai, In re Brouwer* and 35 USC 103(b).

Applicant's arguments have been considered but are found not to be persuasive for the following reasons:

The claimed inventions clearly lack unity, which are not so linked to from a single general inventive concept under PCT rule 13.1, for the following reasons:

An international stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. When claims to different categories are present in the application, the claims will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c),

37 C.F.R. 1.475(b) and (d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).)

Further, according to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as groups 1-17 do not relate to a single general inventive concept because they lack the same or corresponding technical feature. The technical feature of group 2 is a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2, which is shown by WO200112659, having as priority 18 August 1999, to lack novelty, and does not make a contribution over the prior art (See 102(e) rejection below, and MPSRCH search report, 2004, us-09-763-335-2.rag, page 3).

Therefore, the restriction of the polypeptides and polynucleotides is appropriate because the polypeptide of the claimed invention is not a contribution over the prior art, and because the polypeptide is an additional composition.

The restriction of antibodies, and methods of use of the claimed inventions is appropriate because they are additional compositions and methods of use.

Further, since applicant has elected Group 4, the polynucleotide of SEQ ID NO:4, or a polynucleotide encoding the polypeptide of SEQ ID NO:2, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of new claims 33-37 directed to 1) method of screening a compound that binds to the claimed polypeptide (claim 33), 2) method of screening of a compound that alter

expression of the claimed polynucleotide (claim 34), 3) method of assessing toxicity of a test compound (claim 35), 4) method of generating an expression profile of a sample that contains the claimed polynucleotides (claim 37), and 5) a microarray composition have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03. Newly submitted claims 33-37 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The newly added 1) method of screening a compound that binds to the claimed polypeptide (claim 33), 2) method of screening of a compound that alter expression of the claimed polynucleotide (claim 34), 3) method of assessing toxicity of a test compound (claim 35), 4) method of generating an expression profile of a sample that contains the claimed polynucleotides (claim 37), all are separate inventions, and distinct from the invention of group 4, because they are additional methods, and further because the technical feature of the claimed invention is not a contribution over the prior art.

Similarly, the newly added microarray composition (claim 36) is a separate invention, because it is an additional composition, and further because the technical feature of the claimed invention is not a contribution over the prior art.

It is noted that new claims 31, 32 are drawn to the polypeptide encoded by the claimed polynucleotide, and thus belong to non-elected group 2. It is further noted that new claims 38-40 are drawn to an antibody that specifically binds to the polypeptide encoded by the claimed invention, and thus belong to non-elected group 9.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, group 4, Claims 22-28, SEQ ID NO:4, encoding SEQ ID NO:2, are examined in the instant application.

PRIORITY DATE

The Examiner has established a priority date **08/19/1999** for the instantly claimed application serial number 09/76335 as the application 60/150689 to which priority is claimed does not recite the polynucleotide of SEQ ID NO:4, encoding the polypeptide of SEQ ID NO:2 . Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

OBJECTION

Claims 22-26 are objected to because claims 22-26 depend on non-elected claim 21.

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 22-28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility.

Claims 22-28 are drawn to:

1) An isolated polynucleotide comprising the polynucleotide sequence of SEQ ID NO:4 (claims 23, 27), a polynucleotide encoding the polypeptide of SEQ ID NO:2 (claim 22),

2) A naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4 (claim 27), a polynucleotide encoding a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2 (claim 22),

3) A complement of SEQ ID NO:4 or of a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4, or an mRNA equivalent thereof (claim 27),

4) A polynucleotide encoding an immunogenic fragment of a polypeptide consisting of an amino acid sequence of SEQ ID NO:2, wherein said fragment comprises at least 20 contiguous amino acid residues of SEQ ID NO:2 (claim 22), or a polynucleotide comprising at least 60 contiguous nucleotides of the polynucleotide of claim 27 (claim 28),

5) A recombinant polynucleotide comprising a promoter sequence operably linked to the polynucleotide of encoding a polypeptide of claim 21, a cell transformed with said recombinant polynucleotide (claims 24, 25), and

6) A method for producing the polypeptide of claim 21, comprising culturing a cell which is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to the polynucleotide of encoding a polypeptide of claim 21 (claim 26).

The specification discloses that the claimed polynucleotide sequence comprising SEQ ID NO:4 or CSIG-2 (cell signaling protein) is isolated from a brain tumor tissue cDNA library (p.41). The specification further discloses that the utilities for SEQ ID NO:4 or CSIG-2 (cell signaling protein) include diagnosis, prevention and treatment of diseases associated with expression of SEQ ID NO:4, production of and screening of agonists, antibodies and antagonists that specifically bind to SEQ ID NO:2, which is encoded by SEQ ID NO:4 (specification, p.24-27).

However, neither the specification nor any art of record teaches what SEQ ID NO:4 is, what it does do; they do not teach a utility for any of the fragments claimed; they do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. Because of this, the claimed invention lacks substantial utilities, and further experimentation is required to determine what the use is for the claimed polynucleotides.

The asserted utilities for SEQ ID NO:4, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO:4. Additional disclosed utilities for SEQ ID NO:4 include therapy and diagnosis of conditions and diseases characterized by expression

of SEQ ID NO:4. The asserted utility of SEQ ID NO:4 is based on the assertion that:1) SEQ ID NO:2, encoded by SEQ ID NO:4 has chemical and structural homology to Type II EGF (p.14, last two paragraph, bridging p.15), 2) SEQ ID NO:2 has two potential casein kinase phosphorylation sites, three potential protein kinase C phosphorylation sites, and a signal peptide, 3) By Northern analysis, SEQ ID NO:4 is expressed exclusively in brain libraries, 40% of which are associated with cancer (p.15).

It is noted that the specification does not teach how the claimed polynucleotides are "associated with" cancer, or that there are consensus sequences required for the EGF properties or function of the encoded protein. It is further noted that the specification does not disclose that SEQ ID NO:4 is overexpressed in disease tissues as compared to normal tissues.

It is further noted that a sequence similarity search, MPSRCH, shows that SEQ ID NO:2 encoded by the claimed polynucleotides is 28% similar to Fibropellins, encoded by an EGF-repeat containing gene (MPSRCH search report, 2004, us-09-763-335-2.rsp. pages 16-18).

It is clear however that, although there is a 28% identity between an EGF-repeat containing polypeptide and SEQ ID NO:2, there is a 72% dissimilarity between SEQ ID NO:2 and an EGF-repeat containing polypeptide; and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry

out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Biol. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 72% dissimilarity to an EGF-repeat containing polypeptide, the function of the SEQ ID NO:2 could not be predicted, based on sequence similarity with an EGF-repeat containing polypeptide, nor would it be expected to be the same as that of an

EGF-repeat containing polypeptide. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the errror rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of

those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter "downregulated in adenoma". However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al and Scott et al, but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 72% dissimilarity to an EGF-repeat containing polypeptide, the function of the SEQ ID NO:2 could not be predicted, based on sequence similarity with an EGF-repeat containing polypeptide, nor would it be expected to be the same as that of an EGF-repeat containing polypeptide.

Further, even if SEQ ID NO:2 is a an EGF-repeat containing polypeptide-like protein, neither the specification nor any art of record teaches what the polypeptide is, what it does. The specification does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active would function as claimed. Although the specification discloses that the expression of SEQ ID NO:4 is associated with various cancer, there is no disclosure that the claimed polynucleotide is overexpressed in disease tissues as compared to normal tissues, and there is no actual data showing that SEQ ID NO:2 is detected in any tissue. Since SEQ ID NO:2 is an amino acid sequence deduced from SEQ ID NO:2, it is questionable that SEQ ID NO:2 even exists in nature to have any biological activity, including EGF activity .

Thus the claimed invention lacks specific and substantial utilities, and further experimentation is required to determine what the use is for the claimed polynucleotides.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 22-28 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by specific, substantial utility or a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 24-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 22, 24-28 are drawn to:

1) A naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4 (claim 27), a polynucleotide encoding a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:4 (claim 22),

2) A complement of SEQ ID NO:4 or of a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4 (claim 27)

3) A polynucleotide encoding an immunogenic fragment of a polypeptide consisting of an amino acid sequence of SEQ ID NO:2, wherein said fragment comprises at least 20 contiguous amino acid residues of SEQ ID NO:2 (claim 22), or a polynucleotide comprising at least 60 contiguous nucleotides of the polynucleotide of SEQ ID NO:4, its naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4, a complement thereof, or an mRNA equivalent thereof (claim 28).

The polynucleotides recited in claims 22, 24-28 encompass allelic variants of the polynucleotide SEQ ID NO:21, and allelic polynucleotides which encode variants of the polypeptide of SEQ ID NO:8.

In addition, claim 28 encompasses unrelated sequences with unknown structure, that are attached to at least 60 contiguous nucleotides of the polynucleotide of SEQ ID NO:21, a fully complementary sequence thereof, and an RNA equivalent thereof.

Moreover, it is noted that a complement of SEQ ID NO:4 could be a partial or a full length complement of SEQ ID NO:4, wherein a partial complement of SEQ ID NO:4 encompasses unrelated sequences with unknown structure and function, provided they share with SEQ ID NO:4 only a few complementary nucleotides.

Support for variants is provided in the specification on pages 13, 15 where it is disclosed that the invention encompasses variants having at least about 70%, 85% or 95% identity with the polynucleotide sequence encoding the CSIG of SEQ ID NO:2. However, no disclosure of the structure of the claimed naturally occurring variants, i.e. allelic variants having 90% identity with SEQ ID NO:2, or allelic polynucleotides encoding amino acid sequence having at least 90% sequence identity to SEQ ID NO:2, is made in the specification. This is insufficient to support the generic claims .

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that " applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (pages 17-18). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:4, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

In addition, due to the language "comprises", claim 28 encompasses any nucleic acid containing at least 60 contiguous nucleotides of SEQ ID NO:4, which Applicant had not reduced to practice at the time of filing, wherein said nucleic acid could have any sequences attached to at least 60 contiguous nucleotides of SEQ ID NO:4. There is no limitation as to the nature of the molecules attached to at least 60 contiguous nucleotides fragment of SEQ ID NO:4. The present claim encompasses full-length genes and cDNAs that are not further described. There is substantial variability among the species of DNAs encompassed within the scope of the claims because at least 60 contiguous nucleotides of SEQ ID NO:4 is only a fragment of any full-length gene or cDNA species. "A cDNA comprising at least 60 contiguous nucleotides of SEQ ID NO:4"

encompasses a variety of subgenera with widely varying attributes .For example,a cDNA 's principle attribute would include its coding region.A partial cDNA that did not include a disclosure of any open reading frame (ORF)of which it would be a part,would not be representative of the genus of cDNAs because no information regarding the coding capacity of any cDNA molecule would be disclosed.

The following teaching of the court clearly applies to the claimed invention. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA..."requires a precise definition, such as by structure, formula, chemical name, or physical properties", not a mere wish or plan for obtaining the claimed chemical invention".

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotides.

The claims read on polynucleotide variants of SEQ ID NO:4, or nucleotide sequences encoding variants of SEQ ID No:2 , wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length

of the nucleic acid or polypeptide, as well as insertions and deletions, provided that the resulted variation is up to 10% difference with SEQ ID NO:2 or SEQ ID NO:4.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and since the disclosure fails to describe a representative number of species of DNA molecules, the disclosure of a single nucleotide sequence, SEQ ID NO:4, encoding the polypeptide of SEQ ID NO:2 , is insufficient to describe the genus. One of skill in the art would reasonably conclude that Applicant was not in possession of the claimed polynucleotide sequences at the time of filing.

Therefore only an isolated DNA molecule comprising the polynucleotide sequence of SEQ ID NO:4, and polynucleotides encoding SEQ ID NO:2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE OF ENABLEMENT

Claims 22, 24-28 are rejected under 112, first paragraph.

A. If Applicant could overcome the above 101 and 112, first paragraph rejections, Claims 22, 24-28 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide sequence of SEQ ID NO:4, **does not reasonably provide enablement for 1) a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4, or a polynucleotide encoding a naturally occurring amino acid**

sequence at least 90% identical to the amino acid sequence of SEQ ID NO:4, 2) a polynucleotide "comprising" at least 60 contiguous nucleotides of the polynucleotide of SEQ ID NO:4, its naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4, and 3) a complement thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 22, 24-28 are drawn to:

1) A naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4 (claim 27), a polynucleotide encoding a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:4 (claim 22),

2) A complement of SEQ ID NO:4 or of a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4 (claim 27)

3) A polynucleotide encoding an immunogenic fragment of a polypeptide consisting of an amino acid sequence of SEQ ID NO:2, wherein said fragment comprises at least 20 contiguous amino acid residues of SEQ ID NO:2 (claim 22), or a polynucleotide comprising at least 60 contiguous nucleotides of the polynucleotide of SEQ ID NO:4, its naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4, a complement thereof, or an mRNA equivalent thereof (claim 28).

The polynucleotides recited in claims 22, 24-28 encompass allelic variants of the polynucleotide SEQ ID NO:21, and allelic polynucleotides which encode variants of the polypeptide of SEQ ID NO:8.

In addition, claim 28 encompasses unrelated sequences with unknown structure, that are attached to at least 60 contiguous nucleotides of the polynucleotide of SEQ ID NO:21, a complement sequence thereof, and an RNA equivalent thereof.

Moreover, it is noted that a complement of SEQ ID NO:4 could be a partial or a full length complement of SEQ ID NO:4, wherein a partial complement of SEQ ID NO:4 encompasses unrelated sequences with unknown structure and function, provided they share with SEQ ID NO:4 only a few complementary nucleotides.

The scope of the claims 22, 24-28 includes numerous structural variants. Applicant has not shown how to make and use the claimed variants which are capable of functioning or have the properties of the polynucleotide of SEQ ID NO:4.

Further, Applicant has not taught how to make the claimed numerous sequences comprising at least 60 contiguous nucleotides of SEQ ID NO:4 that would be reasonably expected to have the function or properties of SEQ ID NO:4. For example, Applicant has not taught what the structure is for the sequences attached to the at least 60 nucleotides fragment of SEQ ID NO:4, or what the coding regions are for these sequences, or what proteins are encoded by these sequences.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the polypeptide sequences encoded by the claimed variants of SEQ ID NO:4, or polynucleotide sequences comprising at least 60

contiguous nucleotides of SEQ ID NO:4 would have properties related to that of SEQ ID NO:4. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology and that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein, as taught by Bowie et al, Burgess et al, Lazr et al, supra. The above teaching of the art, although drawn to proteins, would apply as well the claimed polynucleotide variants of SEQ ID NO:4, because polynucleotide sequences encode proteins. Thus because on the above unpredictability, one would not know how to make the claimed polynucleotides such that the encoded polypeptides would have the function or properties of the polynucleotide of SEQ ID NO:4.

The specification does not disclose how to make the claimed nucleic acid molecules, such that they would function or have the properties as claimed, or how to use said nucleic acid molecules if they did not have the function or properties claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. If Applicant could overcome the above 101 and 112, first paragraph rejections, Claims 22, 24-26 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO:4, **does not reasonably provide enablement for a polynucleotide "encoding" the polypeptide of SEQ ID NO:2, and a method for producing the polypeptide of claim 21, comprising culturing a cell which is transformed with a recombinant**

polynucleotide comprising a promoter sequence operably linked to the polynucleotide of "encoding" the polypeptide of SEQ ID NO:2 The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 22, 24-26 are drawn to:

1) A polynucleotide encoding the polypeptide of SEQ ID NO:2 (claim 22),

2) A polynucleotide encoding a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:4 (claim 22),

3) A polynucleotide encoding an immunogenic fragment of a polypeptide consisting of an amino acid sequence of SEQ ID NO:2, wherein said fragment comprises at least 20 contiguous amino acid residues of SEQ ID NO:2 (claim 22),

4)) A recombinant polynucleotide comprising a promoter sequence operably linked to the polynucleotide of encoding a polypeptide of claim 21, a cell transformed with said recombinant polynucleotide (claims 24, 25), and

6) A method for producing the polypeptide of claim 21, comprising culturing a cell which is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to the polynucleotide of encoding a polypeptide of claim 21 (claim 26).

There is no disclosure whether the encoded polypeptide of SEQ ID NO:2 is expressed or overexpressed in cancer as compared to adjacent normal control cells.

It is noted that a polynucleotide encoding a polypeptide of SEQ ID NO:2 is not limited to SEQ ID NO:4, but encompasses a genus of sequences that are different from

SEQ ID NO:4 due to degenerate codons, the structure of which could be completely different from SEQ ID NO:4, and are not necessarily detected by the probes specific for SEQ ID NO:4.

One cannot extrapolate the teaching in the specification to the scope of the claims, because it is unpredictable that the degenerate variants of SEQ ID NO:4 would be expressed or overexpressed in cancer tissue as compared to the normal control tissue. It is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type. For example, Schmid S et al, 2001, J comparative Neurology, 430(2): 160-71, teach that the variants flip/flop of the gene GluR are expressed at higher levels in neurons in the auditory braistem, as compared to the wild type GluR-A and GluR-B, and that neurons in the central nucleus of the inferior collicullus express high levels of GluR-B flip but only low levels of the other receptor subunits. Conner et al, 1996, Mol Brain Res, 42: 1-17, teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2). Thus in view of the teaching in the art one cannot predict that the degenerate variants of SEQ ID NO:4 would express or overexpress in cancer tissue as compared to normal control tissue, and therefore, one would not know how to use the claimed degenerate genus of polynucleotides encoding a polypeptide of SEQ ID NO:2.

Further, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Further, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Thus based on the teaching in the art one cannot predict that the polypeptide of SEQ ID NO:2, encoded by the claimed degenerate genus of polynucleotides would express or overexpress in cancer tissue, and therefore, one would not know how to use the polypeptide encoded by the claimed degenerate genus of polynucleotides .

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

C. If Applicant could overcome the above 101 and 112, first paragraph rejections, Claims 25-26 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an "isolated cell" transformed with a recombinant polynucleotide comprising the polynucleotide sequence of SEQ ID NO:4, **does not reasonably provide enablement for "a cell"** transformed with a recombinant polynucleotide comprising the polynucleotide sequence of encoding the

polypeptide of SEQ ID NO:2, and a method for producing the polypeptide of SEQ ID NO:2, comprising culturing said cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 25 is drawn to a cell transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to the polynucleotide of encoding a polypeptide of claim 21. Claim 26 is drawn to a method for producing the polypeptide of SEQ ID NO:2, comprising culturing said cell.

The specification discloses expression vectors derived from viruses, that may be used for delivery of nucleotide sequences to the targeted organ or tissue or cell population, and vectors that are used to introduce antisense sequences into a cell (p.30, third and fourth paragraphs). The specification further discloses administering of vectors capable of expressing the CISG of the claimed invention to treat or prevent disorder associated with decreased of expression or activity of CSIG (p.26, second paragraph).

The claims encompass an in vivo cell from gene therapy, and a method for producing the polypeptide of SEQ ID NO:2, comprising culturing said cell.

The state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene

therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839,

166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

In view of the unpredictability of gene therapy, and the lack of disclosure of how to successfully produce in vivo cells that express the claimed sequence, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application

filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claim 22 is rejected under 35 U.S.C. 102(e) as being anticipated by WO200112659 A2, having as priority 18 August 1999.

Claim 22 is drawn to a polynucleotide encoding a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2.

WO200112659 A2 teaches a nucleic acid sequence encoding a polypeptide having the same length as SEQ ID NO:2 (133 amino acids), and which is 99% similar to SEQ ID NO:2 (MPSRCH search report, 2004, us-09-763-335-2.rag, page 3).

2. Claim 27 is rejected under 35 U.S.C. 102(e) as being anticipated by WO200112659 A2, having as priority 18 August 1999.

Claim 27 is drawn to a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:4, or of a complement thereof, or of an RNA equivalent thereof.

WO200112659 A2 teaches a nucleic acid sequence, which is 96% similar to SEQ ID NO:4, from nucleotide 351 to nucleotide 812 (MPSRCH search report, 2004, us-09-763-335-2.rng, pages 3-4).

Thus the nucleotide sequence taught by WO200112659 A2 seems to be the same as the claimed polynucleotide.

Further, given the polynucleotide sequence taught by WO200112659 A2 , one of ordinary skill in the art would immediately envision the claimed polypeptide comprising

at least 60 contiguous nucleotides of a complement of SEQ ID NO:4, or of an RNA equivalent thereof.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

April 09, 2004